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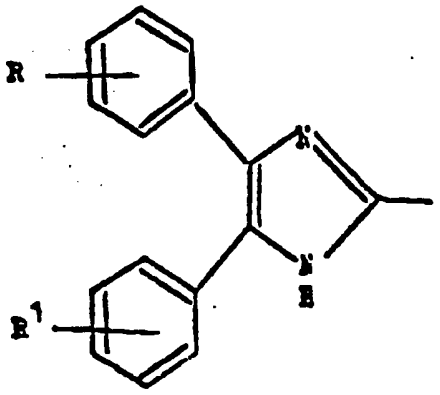

(I)

(57) Abstract

Imidazole derivatives of formula: [DPIM]-$S(O)_p$-W-Y, wherein [DPIM] is of formula (I), wherein R and R^1 each represents hydrogen, halogen, alkyl or alkoxy, p is 0, 1 or 2, W represents alkylene, Y represents an optionally substituted 5- or 6-membered unsaturated ring containing 1 to 4 nitrogen atoms, and pharmaceutically acceptable acid addition salts thereof, are inhibitors of acyl coenzyme-A:cholesterol-O-acyle transferase and of the binding of thromboxane TxA_2 to its receptors and are useful in therapy.

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"2-SUBSTITUTED 4,5-DIPHENYL-IMIDAZOLES"

This invention relates to therapeutically useful imidazole derivatives, to a process for their production, to pharmaceutical compositions containing them, and to their use in a method of treatment of the human or animal body.

In Japanese Patent O.P.I. No. 64-40467 (Application No. 62-196117) there are disclosed inter alia compounds of the general formula (IA) hereinafter depicted, wherein XA represents hydrogen or halogen, or a lower alkyl or lower alkoxy group, m represents 0 or 1, n represents 1, 2, 3 or 4, and RA represents a heterocyclic ring, and their acid addition salts, alone and in association with pharmaceutically acceptable carriers and coatings, and a process for their preparation. The specification states that lower alkyl can have 1 to 6 carbon atoms such as methyl, ethyl, propyl or butyl, and lower alkoxy can be methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, or tert-butoxy etc. containing up to 6 carbon atoms, and the said heterocyclic ring can be pyridyl, pyrimidinyl or imidazolinyl, substituted or unsubstituted with less than 3 substituents, the substituents including methyl, ethyl, n-propyl, iso-propyl, n-butyl, n-pentyl or iso-pentyl etc. with 1 to 6 carbon atoms, halogen or lower alkoxy.

However, in that specification, those compounds are described as having anti-ulcer and anti-inflammatory activity. Nowhere in that specification is there any suggestion that the compounds and their pharmaceutical compositions could be useful as inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase or in the treatment of conditions such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts, or as inhibitors of the binding of thromboxane TxA_2 to its receptors or in the treatment of conditions such as thrombosis and myocardial infarction, vasospastic disorders and bronchospasm or in reperfusion salvage therapy.

In the specification of European Patent Application Publication No. 0301422 A2 there are disclosed <u>inter alia</u> compounds of the general formula:-

$$Het\text{-}S(O)_{nb}\text{-}CH_2\text{-}A \qquad (IB)$$

hereinafter depicted, wherein Het is a 4,5-diphenyl-imidazol-2-yl group , nb is 0 or 1, and A is a group of general formula (IIB) hereinafter depicted, wherein $R_{4'}$, $R_{4''}$ and $R_{4'''}$ are each hydrogen or C_{1-4} alkyl, and physiologically acceptable salts thereof, alone and in association with pharmaceutically acceptable carriers and coatings, and a process for their preparation.

However, in that specification, those compounds are described as having anti-ulcer and gastric acid antisecretory activities. Nowhere in that specification is there any suggestion that the compounds and their pharmaceutical compositions could be useful as inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase or in the treatment of conditions such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts, or as inhibitors of the binding of thromboxane TxA_2 to its receptors or in the treatment of conditions such as thrombosis and myocardial infarction, vasospastic disorders and bronchospasm or in reperfusion salvage therapy.

Thus, the utilities disclosed hereinafter in the present specification are entirely unexpected.

The present invention provides the compounds of the general formula:-

$$[DPIM]\text{-}S(O)_p\text{-}W\text{-}Y \qquad (I)$$

wherein [DPIM] is as hereinafter depicted, wherein R and R^1 are the same or different and each represents a hydrogen or halogen (i.e. fluorine, chlorine, bromine or iodine) atom or a straight- or branched-chain alkyl or alkoxy group containing from 1 to about 6, preferably from 1 to 3 carbon atoms, p represents 0, 1 or 2, W represents a methylene group or an alkylene

chain of 2 to about 6 carbon atoms optionally substituted with one or more straight- or branched-chain alkyl groups of 1 to about 4 carbon atoms, Y represents a 5- or 6-membered unsaturated ring containing 1, 2, 3 or 4 nitrogen atoms, optionally substituted by one or more substituents selected from straight- and branched-chain alkyl groups containing from 1 to about 6 carbon atoms (which are each optionally substituted by a phenyl group), phenyl groups, amino groups and nitro groups, and pharmaceutically acceptable acid addition salts thereof, for use in the preparation of a pharmaceutical composition for the treatment of conditions which can be ameliorated by the administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT; EC 2.3.1.26), such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts, or of an inhibitor of the binding of thromboxane TxA_2 to its receptors, such as thrombosis and myocardial infarction, vasospastic disorders, for example associated with angina, and bronchospasm, for example associated with asthma, or in reperfusion salvage therapy, for example after ischaemic injury.

The present invention also provides a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be

ameliorated by the administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase, such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts, or of an inhibitor of the binding of thromboxane TxA_2 to its receptors, such as thrombosis and myocardial infarction, vasospastic disorders, for example associated with angina, and bronchospasm, for example associated with asthma, or in reperfusion salvage therapy, for example after ischaemic injury, which comprises administering to the patient an effective amount of a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof,as hereinbefore defined, to secure an improvement in the condition of the patient.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable acid addition salt thereof, as hereinbefore defined, for use in a new method of treatment, of the human or animal body, by therapy, of conditions which can be ameliorated by the administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase, such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts, or of an inhibitor of the binding of thromboxane TxA_2 to its receptors, such as thrombosis and myocardial

infarction, vasospastic disorders, for example associated with angina, and bronchospasm, for example associated with asthma, or in reperfusion salvage therapy, for example after ischaemic injury.

The present invention also provides pharmaceutical formulations which contain at least one of the compounds of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, subject to the provisos that (i) when p represents 0 or 1 and W represents an unsubstituted methylene group or an unsubstituted alkylene chain of 2 to 4 carbon atoms, Y represents other than a pyridyl, pyrimidinyl or imidazolinyl group, substituted or unsubstituted with 1 or 2 alkyl groups, R and R^1 being as hereinbefore defined, and (ii) when R and R^1 each represent hydrogen atoms, p represents 0 or 1 and W represents an unsubstituted methylene group, Y represents other than a pyrid-2-yl group, substituted or unsubstituted with 1, 2 or 3 alkyl groups each containing up to 4 carbon atoms, in association with a pharmaceutically acceptable carrier or coating.

The present invention also provides new compounds of formula (I), and pharmaceutically acceptable salts thereof, as hereinbefore defined, subject to the provisos that (i) when p represents 0 or 1 and W represents an unsubstituted methylene group or

an unsubstituted alkylene chain of 2 to 4 carbon atoms, Y represents other than a pyridyl, pyrimidinyl or imidazolinyl group, substituted or unsubstituted with 1 or 2 alkyl groups, R and R^1 being as hereinbefore defined, and (ii) when R and R^1 each represent hydrogen atoms, p represents 0 or 1 and W represents an unsubstituted methylene group, Y represents other than a pyrid-2-yl group, substituted or unsubstituted with 1, 2 or 3 alkyl groups each containing up to 4 carbon atoms.

Especially important features of the present invention are, or involve, compounds of general formula (I) wherein at least one of the symbols has a value selected from the following:-

(i) R represents a hydrogen or fluorine atom or a methyl or methoxy group;

(ii) R^1 represents a hydrogen or fluorine atom or a methyl or methoxy group;

(iii) W represents a methylene or ethylidene group or an alkylene chain of 2 to 6 carbon atoms;

(iv) Y represents an imidazolyl (preferably imidazol-1-yl or imidazol-2-yl), pyrazolyl (preferably pyrazol-1-yl), triazolyl (preferably 1,2,4-triazol-1-yl), tetrazolyl (preferably tetrazol-1-yl or tetrazol—2-yl), pyridyl (preferably pyrid-4-yl) or pyrrolyl (preferably pyrrol-1-yl) group, optionally

substituted by one or two substituents selected from methyl, ethyl, benzyl, phenyl, amino and nitro groups; the other symbols being as hereinbefore defined, and pharmaceutically acceptable acid addition salts thereof.

Preferred acid addition salts are the hydrochlorides and maleates.

Important compounds according to the invention include:

1A 2-[3-(2-methylimidazol-1-yl)propylthio]-4,5-diphenylimidazole and its dihydrochloride

1B 2-[3-(pyrazol-1-yl)propylthio]-4,5-diphenylimidazole and its hydrochloride

1C 2-[2-(1,2,4-triazol-1-yl)ethylthio]-4,5-diphenylimidazole

1D 2-[3-(1,2,4-triazol-1-yl)propylthio]-4,5-diphenylimidazole

1E 2-[4-(1,2,4-triazol-1-yl)butylthio]-4,5-diphenylimidazole

1F 2-[5-(1,2,4-triazol-1-yl)pentylthio]-4,5-diphenylimidazole and its dihydrochloride

1G 2-[2-(imidazol-1-yl)ethylthio]-4,5-diphenylimidazole

1H 2-[3-(imidazol-1-yl)propylthio]-4,5-diphenylimidazole

1I (±)-2-[1-(imidazol-1-yl)ethylthio]-4,5-diphenylimidazole and its dihydrochloride

1J 2-[(1-methylimidazol-2-yl)methylthio]-4,5-diphenylimidazole

1JA 2-[(1-methylimidazol-2-yl)methylthio]-4,5-diphenylimidazole hydrochloride

1K 2-[(1-benzylimidazol-2-yl)methylthio]-4,5-diphenylimidazole

1L 2-[6-(1,2,4-triazol-1-yl)hexylthio]-4,5-diphenylimidazole

1M 2-[4-(2-methylimidazol-1-yl)butylthio]-4,5-diphenylimidazole

1N 2-[3-(2-phenylimidazol-1-yl)propylthio]-4,5-diphenylimidazole

1O 2-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]-4,5-diphenylimidazole

1P 2-[3-(3,5-dimethylpyrazol-1-yl)propylthio]-4,5-diphenylimidazole

1Q 2-[3-(tetrazol-1-yl)propylthio]-4,5-diphenylimidazole

1R 2-[3-(tetrazol-2-yl)propylthio]-4,5-diphenylimidazole

1S 2-[4-(tetrazol-1-yl)butylthio]-4,5-diphenylimidazole

1T 2-[4-(tetrazol-2-yl)butylthio]-4,5-diphenylimidazole

1U 2-[pyrid-4-ylmethylthio]-4,5-diphenylimidazole and its dihydrochloride

2A 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole

2AA 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole dihydrochloride

2B 2-[5-(2-ethylimidazol-1-yl)pentylthio]-4,5-diphenylimidazole

2C 2-[5-(imidazol-1-yl)pentylthio]-4,5-diphenylimidazole,

2D 2-[5-(2-methylimidazol-1-yl)pentylthio]-4,5-diphenylimidazole

2E 2-[6-(2-methylimidazol-1-yl)hexylthio]-4,5-diphenylimidazole

2F 2-[6-(2-ethylimidazol-1-yl)hexylthio]-4,5-diphenylimidazole

2G 2-[5-(pyrazol-1-yl)pentylthio]-4,5-diphenylimidazole

2H 2-[6-(imidazol-1-yl)hexylthio]-4,5-diphenylimidazole

2I 2-[6-(pyrazol-1-yl)hexylthio]-4,5-diphenylimidazole

2J 2-[5-(3-methylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole and 2-[5-(5-methylpyrazol-1-yl)-pentylthio]-4,5-diphenylimidazole

2K 2-[5-(3-amino-5-methylpyrazol-1-yl)pentylthio]-

4,5-diphenylimidazole

2L 2-[5-(4-bromo-3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole

2M 2-[5-(3,5-diphenylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole

2N 2-[5-(pyrrol-1-yl)pentylthio]-4,5-diphenylimidazole

2O 2-[5-(2,5-dimethylpyrrol-1-yl)pentylthio]-4,5-diphenylimidazole

2P 2-[4-(3,5-dimethylpyrazol-1-yl)butylthio]-4,5-diphenylimidazole

2Q 2-[6-(3,5-dimethylpyrazol-1-yl)hexylthio]-4,5-diphenylimidazole

2R 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-fluorophenyl)imidazole

2RA 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-fluorophenyl)imidazole hydrochloride

2S 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methylphenyl)imidazole

2SA 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methylphenyl)imidazole hydrochloride

2T 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methoxyphenyl)imidazole

2U 2-(4,5-diphenylimidazol-2-ylthiomethyl)imidazole

2UA 2-(4,5-diphenylimidazol-2-ylthiomethyl)imidazole dimaleate

2V 4,5-diphenyl-2-[3-(1-methylimidazol-2-yl)propyl-thio]imidazole

2W 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)-sulphonyl]-4,5-diphenylimidazole and

2X 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)-sulphinyl]-4,5-diphenylimidazole.

The letters 1A to 2X are allocated to compounds for easy reference later in this specification.

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT; EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of conditions such as atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts.

They are also inhibitors of the binding of thromboxane TxA_2 to its receptors. They are therefore of utility in the treatment of conditions such as thrombosis and myocardial infarction, vasospastic disorders, for example associated with angina, and bronchospasm, for example associated with asthma, or in reperfusion salvage therapy, for example after ischaemic injury.

Compounds within the scope of the present invention exhibit positive pharmacological activities as demonstrated by the following in-vitro and in-vivo

tests which are believed to correlate to pharmacological activity in humans and other animals.

In in-vitro tests on human platelet membrane, compounds of the invention produced up to 50% inhibition of the binding of thromboxane TxA_2 to its receptors at concentrations down to about 600 nanomolar or less.

In assays performed in-vitro, microsomes, obtained from the livers of rats fed on a diet supplemented with 0.5%w/w cholesterol and 0.25%w/w cholic acid for 7 days, were incubated with radiolabelled oleoyl-CoA in the presence of compounds according to the invention at a concentration of 0.5 or 1 µg/ml. The degree of ACAT inhibition produced is shown in Table 1.

In in-vivo tests, using rats fed on a similar diet to that above and further supplemented by 0.03% w/w of test compound, the compounds according to the invention inhibited increases in plasma cholesterol concentrations, measured after 3 days, relative to control animals fed on the cholesterol supplemented diet without the drug, as shown in Table 1.

Table 1

COMPOUND	In-vitro % Inhibition at 1µg/ml	In-vitro % Inhibition at 0.5µg/ml	In-vivo % Inhibition
1A	90		64
1B	83		
1C	88		
1D	84		
1E	86		53
1F	92		74
1G	86		
1H	80		
1I	53		
1J	85		
1JA	82		23
1K	57		
1L	91		
1M		87	26
1N		57	
1O		82	
1P		87	
1Q	88		
1R	80		
1S		84	41
1T		74	
1U	71		

Compounds of general formula (I) can be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

According to a feature of the invention, compounds of general formula (I), as hereinbefore defined, are prepared by the reaction of a compound of the general formula:-

[DPIM]-SH (II)

or a salt thereof, wherein [DPIM] is as hereinbefore defined, with a compound of formula:

X-W-Y (III)

or a salt thereof, wherein X is a group displaceable by a thiolate salt, such as a halogen e.g. a chlorine, bromine or iodine, atom or an alkyl- or aryl-sulphonyloxy group (e.g. methanesulphonyloxy or 4-toluenesulphonyloxy) and W and Y are as hereinbefore defined. The reaction is generally carried out in an inert organic solvent such as tetrahydofuran or dimethylformamide at a temperature from ambient to 110°C and optionally in the presence of a proton acceptor, such as an amine (e.g. triethylamine).

According to a further feature of the present invention, compounds of general formula (I) are prepared by the interconversion of other compounds of general formula (I). For example, compounds of

formula (I), wherein [DPIM], R, R^1, W and Y are as hereinbefore defined and p represents 1 or 2, are prepared by the oxidation of compounds of formula (I), wherein [DPIM], R, R^1, W and Y are as hereinbefore defined and p is less than in the desired product.

The oxidation may be performed by using a conventional oxidant, such as hydrogen peroxide, sodium metaperiodate, a hypochlorite, an acyl nitrite, sodium perborate, peracids, such as percarboxylic acids (e.g. m-chloroperbenzoic acid), potassium permanganate or potassium hydrogen persulphate, or a ruthenium (VIII) compound, in an inert solvent, at or below room temperature. Ruthenium (VIII) compounds can conveniently be prepared in situ by the oxidation of ruthenium (III) compounds, for example by means of a percarboxylic acid (e.g. m-chloroperbenzoic acid).

Suitable solvents may include water, alcohols, water-alcohol mixtures, chlorinated hydrocarbons, such as dichloromethane, and organic acids.

Compounds of general formula (I) wherein p is 1, the other symbols being as hereinbefore defined, may be obtained in a chirally pure form by separation of the enantiomers arising from a non-selective oxidation or by using known enantio-selective oxidising systems.

By the term "pharmaceutically acceptable salts" as used in this specification is meant salts the anions

of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmaceutical properties of the parent compounds of general formula (I) are not vitiated by side-effects ascribable to those anions.

Suitable acid addition salts for use in pharmaceuticals may be selected from salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates, sulphates and nitrates, and organic acids, for example oxalates, lactates, tartrates, acetates, salicylates, citrates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates and di-p-toluoyltartrates.

According to a further feature of the invention, salts of compounds of formula (I) are prepared by reaction of the parent compounds of formula (I) with the appropriate acid, by the application or adaptation of known methods.

As well as being useful in themselves as active compounds, salts of compounds of formula (I) are useful for the purposes of purification of the parent compounds of formula (I), for example by exploitation of the solubility differences between the salts and the parent compounds, by techniques well known to those skilled in the art.

The parent compounds of formula (I) can be regenerated from their salts by the application or adaptation of known methods.

For example, parent compounds of general formula (I) can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

In this specification reference to compounds of formula (I) is intended to include reference to their pharmaceutically acceptable salts, where the context so permits.

The starting materials and intermediates can be prepared by the application or adaptation of known methods.

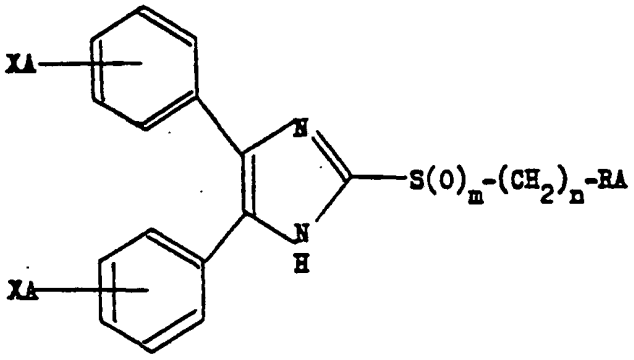
Compounds of formula (I) can be purified by the usual physical means, for example by crystallisation or chromatography.

The following Examples illustrate the preparation of the compounds according to the invention.

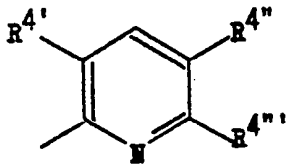
N.M.R. spectra were recorded at 200MHz or 400MHz. Chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances:-

s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets.

Infra-red spectra were recorded in potassium bromide discs. The positions of the major absorption peaks are given.



(IA)



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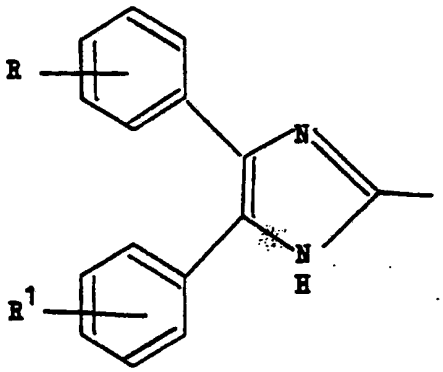


(DPIM)

EXAMPLE 1

Compounds 1A to 1H and 1L to 1P

i) Sodium hydride (80% dispersion in oil, 1.65g, 50mmol) was added to a stirred solution of 2-methyl-imidazole (4.1g, 50mmol) in anhydrous dimethylformamide (50ml) with ice cooling. After stirring for 30min 1-bromo-3-chloro-propane (7.9g, 50mmol) was added and the mixture allowed to stir at room temperature overnight. Evaporation of the mixture gave a colourless semisolid which was partitioned between ether (150ml) and water (100ml). The layers were separated and the ether layer washed with water (3x50ml), dried ($MgSO_4$) and evaporated to give 1-(3-chloropropyl)-2-methyl-imidazole (2.3g), as a colourless oil.

Potassium t-butoxide (1.56g, 14mmol) was added to a stirred solution of 4,5-diphenylimidazole-2-thiol (3.5g, 14mmol) in anhydrous dimethylformamide (50ml). After stirring at room temperature for 30min, 1-(3-chloro-propyl)-2-methylimidazole (2.3g, 15mmol) was added and the mixture stirred at room temperature overnight. The mixture was evaporated to dryness and the residue partitioned between ethyl acetate (150ml) and water (50ml). The layers were separated and the organic layer was washed with water (50m), dried ($MgSO_4$) and evaporated. The resulting semisolid was

purified by flash chromatography (10% ethanol in ethyl acetate) to give 2-[3-(2-methylimidazol-1-yl)propylthio]-4,5-diphenylimidazole as a white solid.

A solution of the solid in ethanol (30ml) was added to a stirred solution of hydrogen chloride in ethanol [prepared by adding acetyl chloride (20ml) dropwise to cold (10°C) ethanol (90ml), with stirring, maintaining the temperature below 30°C] and the mixture stirred at room temperature for 2hr. Evaporation gave a white solid, which was triturated with ether and collected by filtration to give 2-[3-(2-methylimidazol-1-yl)propylthio]-4,5-diphenylimidazole dihydrochloride (1.9g), as a white solid, m.p. 252-253°C;

[Found:- C, 59.0; H, 5.4; N, 12.6; Cl, 15.6; S, 7.3%

Calculated for $C_{22}H_{22}N_4S.2HCl$:- C, 59.1; H, 5.4; N, 12.5; Cl, 15.9; S, 7.2%

N.M.R. (200MHz; CD_3SOCD_3): 2.19 (2H, m), 2.67 (3H, s), 3.49 (2H, t, J=7Hz), 4.29 (2H, t, J=6Hz), 7.40-7.60 (11H, m), 7.78 (1H, d, J=2Hz)

IR (KBr): 775, 1506, 2510, 2643, 3432 cm^{-1}].

By proceeding in a similar manner, but replacing the 2-methylimidazole by the appropriate azole and the 1-bromo-3-chloropropane by the appropriate dihalide, and with the salt formation step being optional, there were prepared:-

ii) 2-[3-(pyrazol-1-yl)propylthio]-4,5-diphenylimidazole hydrochloride, m.p. 174-175°C;

iii) 2-[2-(1,2,4-triazol-1-yl)ethylthio]-4,5-diphenylimidazole, m.p. 144-145°C;

iv) 2-[3-(1,2,4-triazol-1-yl)propylthio]-4,5-diphenylimidazole, m.p. 127-129°C;

v) 2-[4-(1,2,4-triazol-1-yl)butylthio]-4,5-diphenylimidazole, m.p. 117-118°C;

vi) 2-[5-(1,2,4-triazol-1-yl)pentylthio]-4,5-diphenylimidazole dihydrochloride, m.p. 253-254°C;

vii) 2-[2-(imidazol-1-yl)ethylthio]-4,5-diphenylimidazole, m.p. 172-173°C;

viii) 2-[3-(imidazol-1-yl)propylthio]-4,5-diphenylimidazole, m.p. 184°C;

ix) 2-[6-(1,2,4-triazol-1-yl)hexylthio]-4,5-diphenylimidazole, m.p. 69-70°C;

x) 2-[4-(2-methylimidazol-1-yl)butylthio]-4,5-diphenylimidazole, m.p. 168-169°C;

xi) 2-[3-(2-phenylimidazol-1-yl)propylthio]-4,5-diphenylimidazole, m.p. 142-145°C;

xii) 2-[2-(2-methyl-5-nitroimidazol-1-yl)ethylthio]-4,5-diphenylimidazole, m.p. 217-220°C; and

xiii) 2-[3-(3,5-dimethylpyrazol-1-yl)propylthio]-4,5-diphenylimidazole, m.p. 119-120°C.

EXAMPLE 2

Compound 1I

Potassium t-butoxide (7.84g, 70mmol) was added to a stirred solution of 4,5-diphenylimidazole-2-thiol (5.0g, 20mmol) in anhydrous dimethylformamide (100ml). After stirring at room temperature for 30min, (±)-1-(1-chloroethyl)imidazole hydrochloride (7.3g, 44mmol) was added and the mixture stirred at room temperature overnight. Work up and purification by flash chromatography (25% methanol in ethyl acetate) as in Example 1(i) gave the free base as an orange oil. This was converted to the hydrochloride as in Example 1(i) to give (±)-2-[1-(imidazol-1-yl)ethylthio]-4,5-diphenylimidazole dihydrochloride (2.5g), as an off-white powder, m.p. 169-170°C;

[Found:- C, 55.2; H, 5.0; N, 12.5; Cl, 15.7; S, 7.4%

Calculated for $C_{20}H_{18}N_4S.2HCl.H_2O$:- C, 54.9; H, 5.0; N, 12.8; Cl, 16.2; S, 7.3%

N.M.R. (200MHz; CD_3SOCD_3): 2.04 (3H, d, J=8Hz), 6.53 (1H, q, J=8Hz), 7.40-7.55 (10H, m), 7.80 (1H, d, J=2Hz), 8.07 (1H, d, J=2Hz), 9.49 (1H, s,)

IR (KBr): 696, 766, 2637, 2697, 2713, 2800, 2828 cm^{-1}].

EXAMPLE 3

Compounds 1J, 1JA, 1K and 1U

i) Sodium hydride (80% dispersion in oil, 3.27g, 100mmol) was added to a stirred suspension of 4,5-diphenylimidazole-2-thiol (13.8g, 54mmol) in anhydrous tetrahydrofuran (150ml). The mixture was stirred at 60°C until complete solution occurred. 1-Methyl-2-chloromethylimidazole hydrochloride (10.0g, 60mmol) was added and the mixture stirred at reflux overnight. After cooling to room temperature the mixture was poured into water (500ml) and the cream precipitate collected by filtration. Recrystallisation from isopropanol gave 2-[(1-methylimidazol-2-yl)methylthio]-4,5-diphenylimidazole (12.2g), as a yellow powder, m.p. 189-190°C; [Found:- C, 69.2; H, 5.3; N, 16.3; S, 9.1%; Calculated for $C_{20}H_{18}N_4S$:- C, 69.3; H, 5.2; N, 16.2; S, 9.3.%

N.M.R. (400MHz; $CDCl_3$): 3.68 (3H, s), 4.24 (2H, s), 6.94 (1H, d, J=2Hz), 7.01 (1H, d, J=2Hz), 7.20-7.60 (10H, m,)

IR (KBr): 689, 764, 1439, 1644, 3406 cm^{-1}].

ii) The free base was converted to the hydrochloride salt as in Example 1(i), m.p. 216-221°C;

[Found:- C, 55.1; H, 5.0; N, 13.0; Cl, 15.9; S, 7.4; H_2O, 4.3%

Calculated for $C_{20}H_{18}N_4S.2HCl.H_2O$: C, 54.9; H, 5.1; N, 12.8; Cl, 16.2; S, 7.3; H_2O, 4.1%].

iii) By proceeding in the same manner as part (i), but replacing the 1-methyl-2-chloromethylimidazole hydrochloride by 1-benzyl-2-chloromethylimidazole hydrochloride, there was prepared 2-[(1-benzylimidazol-2-yl)methylthio]-4,5-diphenylimidazole, m.p. 181-183°C;

[Found:- C, 73.8; H, 5.2; N, 13.3; S, 7.4%

Calculated for $C_{26}H_{22}N_4S$:- C, 73.9; H, 5.3; N, 13.3; S, 7.6%

N.M.R. (200MHz; $CDCl_3$): 4.20 (2H, s), 5.20 (2H, s), 6.92 (1H, d, J=2Hz), 7.07 (1H, d, J=2Hz), 7.10-7.60 (15H, m)

IR (KBr): 687, 1110, 1490 cm^{-1}].

iv) By proceeding in the same manner as part (i), but replacing the 1-methyl-2-chloromethylimidazole hydrochloride by 4-chloromethylpyridine hydrochloride and carrying out the reaction in the presence of triethylamine, there was prepared 2-[pyrid-4-ylmethylthio]-4,5-diphenylimidazole.

This was converted to the hydrochloride salt as in Example 1(i) to give 2-[pyrid-4-ylmethylthio]-4,5-diphenylimidazole dihydrochloride, m.p. 225-227°C;

[Found:- C, 60.3; H, 4.56; N, 10.1; S, 7.6; Cl, 17.0%

Calculated for $C_{21}H_{17}N_3S.2HCl$:- C, 60.57; H, 4.59; N, 10.09; S, 7.7; Cl, 17.0%].

EXAMPLE 4

Compounds 1Q to 1T

i) A solution of tetrazole (5.8g) in anhydrous dimethylformamide (75ml) was cooled in an ice bath and carefully treated with sodium hydride (80% dispersion in oil, 2.5g). After stirring for 30min, 1-bromo-3-chloropropane (13.0g) was added and the mixture stirred at room temperature overnight. Evaporation of the mixture gave a colourless semisolid which was partitioned between water (100ml) and ethyl acetate (100ml). The layers were separated and the organic layer washed with water (50ml), dried ($MgSO_4$) and evaporated to give a mixture of 1-(3-chloropropyl)-tetrazole and 2-(3-chloropropyl)tetrazole (11.5g).

Potassium t-butoxide (2.24g) was added to a stirred solution of 4,5-diphenylimidazole-2-thiol (5.04g) in anhydrous dimethylformamide (75ml). After stirring at room temperature for 10min, the mixture of 1-(3-chloropropyl)tetrazole and 2-(3-chloropropyl)-tetrazole (3.3g) in dimethylformamide (5ml) was added and the mixture stirred at room temperature overnight. The mixture was evaporated to dryness and the residue

partitioned between ethyl acetate (150ml) and water (75ml). The layers were separated and the organic layer was washed with water (75ml), dried ($MgSO_4$) and evaporated to give a yellow solid. TLC analysis (silica gel plates, ethyl acetate eluent) showed two components, rf0.4 and 0.7. The mixture was purified by flash chromatography (ethyl acetate) to give two fractions.

The faster running fraction was purified by flash chromatography (4:1 dichloromethane / ethyl acetate as eluent) to give 2-[3-(tetrazol-1-yl)propyl-thio]-4,5-diphenylimidazole (1.8g), as a white solid, m.p. 98-99°C; [Found:- C,63.2;H,5.00;N,23.0;S,8.8%; Calculated for $C_{19}H_{18}N_6S$:- C,62.95;H,5.01;N,23.19; S,8.85%].

The slower running fraction was recrystallised from ethyl acetate to give 2-[3-(tetrazol-2-yl)propyl-thio]-4,5-diphenylimidazole (1.8g), as a white crystalline solid, m.p. 162-163°C; [Found:- C,62.7; H,4.9;N,23.3;S,8.9%; Calculated for $C_{19}H_{18}N_6S$:- C,62.95;H,5.01;N,23.19;S,8.85%].

ii) By proceeding in a similar manner, but replacing the 1-bromo-3-chloropropane by 1-chloro-4-bromobutane, there were prepared:-

2-[4-(tetrazol-1-yl)butylthio]-4,5-diphenyl-imidazole, m.p. 125-126°C; and

2-[4-(tetrazol-2-yl)butylthio]-4,5-diphenyl-imidazole, m.p. 133-134°C.

EXAMPLE 5

Compounds 2A to 2I

A stirred solution of 3,5-dimethylpyrazole (9.6g) in anhydrous dimethylformamide (100ml), cooled in an ice-bath, was treated with potassium tert-butoxide (11.2g). The ice-bath was removed and the mixture was stirred for one hour, the temperature rising to room temperature. The mixture was then treated with 1-bromo-5-chloropentane (18.6g), and the mixture was stirred at room temperature overnight, to give "reaction mixture 1".

A mixture of 4,5-diphenylimidazole-2-thiol (25.2g) and potassium tert-butoxide (11.2g) in anhydrous dimethylformamide (200ml) was stirred at room temperature for 30 minutes. This mixture was treated with "reaction mixture 1", and stirred at room temperature overnight. The mixture was filtered and the filtrate was evaporated to low bulk, and treated with dichloromethane (400ml) and water (200ml). The organic layer was washed with water (200ml), dried over magnesium sulphate, and evaporated. The resulting residue was triturated with diethyl ether (250ml), and filtered. The filtrate was evaporated and the resulting residue was subjected to flash chromatography on a silica gel column, using a mixture of ethyl acetate and dichloromethane (1:1v/v) as eluent. The

resulting product was triturated with pentane, to give 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole (16.9g), in the form of a white solid, m.p. 75°C. [Elemental analysis:- C,71.9;H,6.78;N,13.5;S,8.0%; calculated:- C,72.1; H,6.73;N,13.5;S,7.69%].

By proceeding in a similar manner, but replacing the 3,5-dimethylpyrazole, used as a starting material, by the corresponding quantity of the appropriate imidazole or the appropriate pyrazole, or derivative thereof, and replacing where necessary the 1-bromo-5-chloropentane, used as a starting material, by the corresponding quantity of the appropriate dihaloalkane, there were prepared:-

2-[5-(2-ethylimidazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 90°C;

2-[5-(imidazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 120°C;

2-[5-(2-methylimidazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 120°C;

2-[6-(2-methylimidazol-1-yl)hexylthio]-4,5-diphenylimidazole, m.p. 110°C;

2-[6-(2-ethylimidazol-1-yl)hexylthio]-4,5-diphenylimidazole, m.p. 105°C;

2-[5-(pyrazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 120°C;

2-[6-(imidazol-1-yl)hexylthio]-4,5-diphenylimidazole, m.p. 110°C; and

2-[6-(pyrazol-1-yl)hexylthio]-4,5-diphenylimidazole, m.p. 135°C.

EXAMPLE 6

Compounds 2J to 2T

A stirred solution of 3-methylpyrazole (10g) in anhydrous tetrahydrofuran (300ml) under nitrogen was carefully treated with sodium hydride (60% dispersion in oil, 6.7g). After stirring for 30 minutes at room temperature the mixture was treated with 1-bromo-5-chloropentane (23.4g), and the mixture was heated at reflux overnight, and then it was allowed to cool to room temperature. The resulting mixture was added to a stirred suspension of the sodium salt of 4,5-diphenylimidazole-2-thiol in anhydrous tetrahydrofuran [prepared by carefully treating a suspension of 4,5-diphenylimidazole-2-thiol (30.7g) in anhydrous tetrahydrofuran (300ml), under nitrogen, with sodium hydride (60% dispersion in oil, 5.7g) and stirring at room temperature for one hour] and the whole was heated at reflux overnight. Evaporation, followed by treatment with a mixture of ethyl acetate and water (500ml;1:1v/v), separation of the organic phase and subsequent concentration, gave a brown oil. This brown oil was treated with aqueous hydrochloric

acid (800ml;2N) and charcoal (2g) at 90°C and the mixture was filtered. The filtrate was basified by addition of solid potassium carbonate, and was extracted four times with dichloromethane (300ml). The combined dichloromethane extracts were dried over magnesium sulphate and evaporated, and the residue was purified by flash chromatography on silica gel (using a mixture of ethyl acetate and cyclohexane, 1:2v/v as eluent). The major component was triturated with pentane and then with diethyl ether, to give a mixture of 2-[5-(3-methylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole and 2-[5-(5-methylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole (14.5g; ratio approximately 3:5) in the form of a white solid, m.p. 114-116°C; [Elemental analysis:- C, 71.6; H, 6.47; N, 14.1; S, 8.0%; Calculated:- C, 71.6; H, 6.5; N, 13.9; S, 7.96%].

By proceeding in a similar manner, but replacing the 3-methylpyrazole, used as a starting material, by the corresponding quantities of the appropriate azoles, there were prepared:-

2-[5-(3-amino-5-methylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p.60-62°C, [Elemental analysis:- C, 68.7; H, 6.46; N, 16.6%; Calculated:- C, 69.0; H, 6.51; N, 16.77%];

2-[5-(4-bromo-3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-

diphenylimidazole, m.p.122-124°C; [Elemental analysis:- C, 60.7; H, 5.46; N, 11.2; S, 6.42%; Calculated:- C, 60.6; H, 5.5; N, 11.3; S, 6.4%]; 2-[5-(3,5-diphenylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p.148-150°C; 2-[5-(pyrrol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 132-134°C; [Elemental analysis:- C, 74.6; H, 6.54; N, 11.0; S, 8.3%; Calculated:- C, 74.37; H, 6.5; N, 10.84; S, 8.27%]; 2-[5-(2,5-dimethylpyrrol-1-yl)pentylthio]-4,5-diphenylimidazole, m.p. 122-124°C; [Elemental analysis:- C, 74.8; H, 6.97; N, 9.9; S, 8.0%; Calculated:- C, 75.14; H, 7.03; N, 10.11; S, 7.71%];

By again proceeding in a similar manner, but replacing the 3-methylpyrazole by 3,5-dimethylpyrazole, and replacing the 1-bromo-5-chloropentane by the appropriate dihalide, there were prepared:- 2-[4-(3,5-dimethylpyrazol-1-yl)butylthio]-4,5-diphenylimidazole, m.p.172-175°C; [Elemental analysis:- C, 71.6; H, 6.59; N, 13.9; S, 7.9%; Calculated:- C, 71.6; H, 6.5; N, 13.9; S, 7.96%]; 2-[6-(3,5-dimethylpyrazol-1-yl)hexylthio]-4,5-diphenylimidazole, as a colourless viscous liquid.

By again proceeding in a similar manner, but replacing the 3-methylpyrazole by 3,5-dimethylpyrazole and replacing the 4,5-diphenylimidazole-2-thiol by the

appropriate 4,5-diphenylimidazole-2-thiol, there were prepared:-

2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-fluorophenyl)imidazole, as a viscous gum;

2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methylphenyl)imidazole, as a viscous gum; and

2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methoxyphenyl)imidazole, m.p.133-136°C.

EXAMPLE 7

Compounds 2RA and 2SA

2-[5-(3,5-Dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-fluorophenyl)imidazole was dissolved in anhydrous tetrahydrofuran and treated with excess ethereal hydrogen chloride. Evaporation of this solution, trituration of the residue with toluene and then with diethyl ether, followed by crystallisation from a mixture of ethanol, acetone and diethyl ether, gave 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-fluorophenyl)imidazole hydrochloride as a white solid, m.p.159-162°C; [Elemental analysis:- C, 57.0; H, 5.5; N, 10.8; Cl, 13.6; S, 6.56%; Calculated for $C_{25}H_{26}F_2N_4S.2HCl$:- C, 57.1; H,5.37; N, 10.7; Cl, 13.5; S, 6.1%].

By proceeding in a similar manner, but crystallising from a mixture of ethanol and diethyl ether, 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-

(bis-4-methylphenyl)imidazole was converted to 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-(bis-4-methylphenyl)imidazole hydrochloride as a white solid, m.p. 144-149°C.

EXAMPLE 8

Compound 2AA

2-[5-(3,5-Dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole was dissolved in anhydrous tetrahydrofuran and treated with excess ethereal hydrogen chloride. Evaporation of this solution, followed by trituration of the residue with diethyl ether, gave 2-[5-(3,5-dimethylpyrazol-1-yl)pentylthio]-4,5-diphenylimidazole dihydrochloride, m.p.198-200°C.

EXAMPLE 9

Compound 2U

A mixture of 2-chloromethylimidazole hydrochloride (1.9g) and 4,5-diphenylimidazole-2-thiol (3.48g) in dimethylformamide (50ml) was heated at 100-110°C for 90 minutes and was then it was poured into water (300ml). The solid which precipitated was removed by filtration and the filtrate was treated with sodium hydrogen carbonate (3.1g), to give a precipitate. This precipitate was washed with water, and then recrystallised from ethanol, to give 2-(4,5-diphenylimidazol-2-ylthiomethyl)imidazole (2.5g), in the form of a white solid, m.p. 220-222°C.

EXAMPLE 10

Compound 2UA

A solution of maleic acid (1.68g) in ethyl acetate (50ml) was added to a boiling suspension of 2-(4,5-diphenylimidazol-2-ylthiomethyl)imidazole (2.45g) in ethyl acetate (200ml) and butan-2-one (100ml), producing a clear solution. The solution was concentrated under reduced pressure to about 50ml, returned to the boil, and treated with acetone, to give a clear solution, which was allowed to cool, to give 2-(4,5-diphenylimidazol-2-ylthiomethyl)imidazole dimaleate, in the form of white crystals; m.p. 160-162°C (with decomposition).

EXAMPLE 11

Compound 2V

2-(3-Hydroxypropyl)-1-methylimidazole (2.6g) was carefully treated with thionyl chloride (10ml), cooling in an ice-bath, and the resulting solution was left at room temperature for 3 days. Excess thionyl chloride was then removed under reduced pressure, and the residue was treated with dry toluene, to give a sticky solid, which was dried at 60°C/20mmHg. It was then dissolved in dry dimethylformamide (80ml) and treated with 4,5-diphenylimidazole-2-thiol (2.68g), and the mixture was heated at 120-140°C for 4 hours. The mixture was then cooled to 100°C and was then poured

into a mixture of water (300ml) and hydrochloric acid (50ml;1N). The solid which precipitated was washed with water, and then it was discarded. The combined filtrate was basified to pH8 and the resulting precipitate was collected, washed with water, and crystallised from acetone, to give 4,5-diphenyl-2-[3-(1-methylimidazol-2-yl)propylthio]imidazole (1.81g), in the form of colourless needles, m.p. 174-176°C.

EXAMPLE 12

Compound 2W

A suspension of 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)thio]-4,5-diphenylimidazole (5.0g) in a mixture of dichloromethane (75ml) and water (75ml) was stirred at room temperature for 30 minutes. The mixture was then cooled to 5°C treated with a solution of sodium metaperiodate (10.9g) in water (25ml), followed immediately by ruthenium (III) chloride trihydrate (0.03g). The mixture was stirred at 5°C for 30 minutes and then it was treated carefully with solid sodium hydrogen carbonate (5.0g) and dichloromethane (100ml). The aqueous layer was extracted with dichloromethane (2x50ml). The combined extracts were layers were washed with water (2x50ml), dried over magnesium sulphate and evaporated, to give a dark oil. This oil was subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate

and cyclohexane (1:1v/v), followed by trituration with diethyl ether, to give 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)sulphonyl]-4,5-diphenylimidazole (1.5g) as a white powder, m.p. 142-144°C. [Elemental analysis:- Found:- C,67.2;H,6.35;N,12.5;S,7.2%; calculated:- C,66.93;H,6.29;N,12.49;S,7.14%;].

EXAMPLE 13

A stirred solution of 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)thio]-4,5-diphenylimidazole (5.0g) in dichloromethane (250ml), cooled with in an acetone/ice bath (internal temperature -10 to -5°C) was treated with sodium hydrogen carbonate (2.0g), followed by 3-chloroperoxybenzoic acid (50-60%; 3.4g). After 35 minutes stirring in the cooling bath, the mixture was treated with sodium bicarbonate (5.0g) and dichloromethane (200ml). The organic layer was washed successively with saturated aqueous sodium metabisulphite solution (4x100ml), saturated aqueous sodium bicarbonate solution (100ml) and water (2x100ml), dried over magnesium sulphate and evaporated, to give a dark oil, which was subjected to flash chromatography on silica gel, eluting with a mixture of ethyl acetate and methanol (9:1v/v), to give 2-[(5-(3,5-dimethylpyrazol-1-yl)pent-1-yl)sulphinyl]-4,5-diphenylimidazole (1.2g) as an amorphous solid, m.p. 38-40°C.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula (I) or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also

include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Compositions according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula (I) or a pharmaceutically acceptable salt thereof.

The percentage of active ingredient in the compositions of the invention may be varied, it being

necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration, the duration of the treatment and the condition of the patient. In the adult, the doses are generally from 0.01 to 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from 0.001 to 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration.

The following Example illustrates a pharmaceutical composition according to the present invention.

COMPOSITION EXAMPLE

No. 2 size gelatin capsules each containing:-

2-[5-(1,2,4-triazol-1-yl)pentylthio]-4,5-di-phenylimidazole dihydrochloride	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

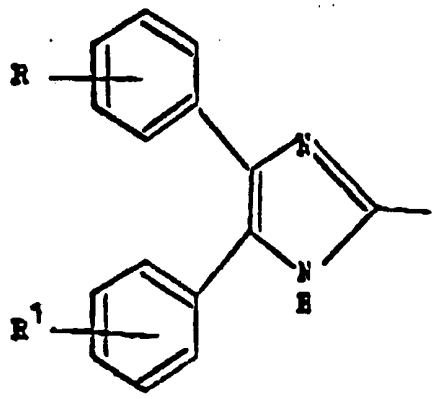
were prepared in accordance with the usual procedure.

CLAIMS

1. An imidazole derivative of the general formula :

$$[DPIM]\text{-}S(O)_p\text{-}W\text{-}Y \qquad I$$

wherein [DPIM] is of the general formula :



(DPIM)

wherein R and R^1 are the same or different and each represents a hydrogen or halogen atom or a straight- or branched-chain alkyl or alkoxy group containing from 1 to 6 carbon atoms, p represents 0, 1 or 2, W represents a methylene group or an alkylene chain of 2 to 6 carbon atoms optionally substituted with one or more straight- or branched-chain alkyl groups of 1 to 4 carbon atoms, Y represents a 5- or 6-membered unsaturated ring containing 1, 2, 3 or 4 nitrogen atoms, optionally substituted by one or more substituents selected from straight- and branched-chain alkyl groups containing from 1 to 6 carbon atoms (which are each optionally substituted by a phenyl group), phenyl groups, amino groups and nitro groups, and

pharmaceutically acceptable acid addition salts thereof, for use in the preparation of a pharmaceutical composition for the treatment of a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase or of an inhibitor of the binding of thromboxane TxA_2 to its receptors.

2. A compound according to claim 1 for use in the preparation of a pharmaceutical composition for the treatment of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease, atheroma in vein grafts, thrombosis, myocardial infarction, a vasospastic disorder, bronchospasm, or in reperfusion salvage therapy.

3. An imidazole derivative of general formula I, as defined in claim 1, or a pharmaceutically acceptable acid addition salt thereof, subject to the provisos that (i) when p represents 0 or 1 and W represents an unsubstituted methylene group or an unsubstituted alkylene chain of 2 to 4 carbon atoms, Y represents other than a pyridyl, pyrimidinyl or imidazolinyl group, substituted or unsubstituted with one or two alkyl groups, R and R^1 being as defined in claim 1, and (ii) when R and R^1 each represent hydrogen atoms, p represents 0 or 1 and W represents an unsubstituted methylene group, Y represents other than a pyrid-2-yl group, substituted or unsubstituted with 1, 2 or 3 alkyl groups each containing up to 4 carbon atoms, for use in a method of treatment of the human or

animal body by therapy.

4. A compound according to claim 3 for use in a method of treatment of the human or animal body by therapy of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease, atheroma in vein grafts, thrombosis, myocardial infarction, a vasospastic disorder, bronchospasm, or in reperfusion salvage therapy.

5. An imidazole derivative of general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof, provided that :
(i) when p represents 0 or 1 and W represents an unsubstituted methylene group or an unsubstituted alkylene chain of 2 to 4 carbon atoms, Y represents other than a pyridyl, pyrimidinyl or imidazolinyl group, substituted or unsubstituted with one or two alkyl groups, R and R^1 being as defined in claim 1, and (ii) when R and R^1 each represent hydrogen atoms, p represents 0 or 1 and W represents an unsubstituted methylene group, Y represents other than a pyrid-2-yl group, substituted or unsubstituted with 1, 2 or 3 alkyl groups each containing up to 4 carbon atoms.

6. A compound according to claim 5 wherein alkyl and alkoxy groups within the definitions of R and R^1 contain from 1 to 3 carbon atoms.

7. A compound according to claim 5 or 6 wherein at least one of the symbols has a value selected from the

following :

(i) R represents a hydrogen or fluorine atom or a methyl or methoxy group;

(ii) R^1 represents a hydrogen or fluorine atom or a methyl or methoxy group;

(iii)W represents a methylene or ethylidene group or an alkylene chain of 2 to 6 carbon atoms;

(iv) Y represents an imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl or pyrrolyl group, optionally substituted by one or two substituents selected from methyl, ethyl, benzyl, phenyl, amino and nitro groups.

8. A compound according to claim 7 wherein Y represents an imidazol-1-yl, imidazol-2-yl, pyrazol-1-yl, 1,2,4-triazol-1-yl, tetrazol-1-yl, tetrazol-2-yl, pyrid-4-yl, or pyrrol-1-yl group optionally substituted by one or two substituents from methyl, ethyl, benzyl, phenyl, amino and nitro groups.

9. A compound according to claim 5 hereinbefore identified as any one of compounds 1A to 2X.

10. A process for the preparation of a compound of general formula I as defined in claim 5 which comprises:

(A) the reaction of a compound of the general formula:

[DPIM]-SH II

or a salt thereof, wherein [DPIM] is as defined in claim 5, with a compound of the general formula :

X-W-Y III

or a salt thereof, wherein X is a group displaceable by a thiolate salt and W and Y are as defined in claim 5;

(B) when [DPIM], R, R^1, W and Y are as defined in claim 5 and p represents 1 or 2, the oxidation of a compound of general formula I wherein [DPIM], R, R^1, W and Y are as defined in claim 5 and p is less than in the desired product;

optionally followed by the conversion of a compound of general formula I into a pharmaceutically acceptable acid addition salt thereof.

11. A pharmaceutical composition which comprises an imidazole derivative of general formula I as defined in claim 5, or a pharmaceutically acceptable acid addition salt thereof, in association with a pharmaceutically acceptable carrier or coating.

12. A pharmaceutical composition useful in the treatment of a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase or an inhibitor of the binding of thromboxane TxA_2 to its receptors which comprises an amount effective to ameliorate said condition of an imidazole derivative of general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt thereof.

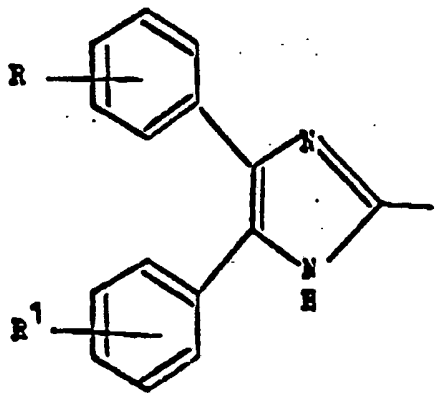
13. A method for the treatment of a human or

animal host suffering from, or subject to, a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase or of an inhibitor of the binding of thromboxane TxA_2 to its receptors which comprises the administration to said host of an imidazole derivative of general formula I as defined in claim 1 or a pharmaceutically acceptable acid addition salt.

14. An agent for use in the treatment of a condition which can be ameliorated by administration of an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase or of an inhibitor of the binding of thromboxane TxA_2 to its receptors which comprises an imidazole derivative of the general formula :

$$[DPIM]\text{-}S(O)_p\text{-}W\text{-}Y \qquad I$$

wherein [DPIM] is of the general formula :



(DPIM)

wherein R and R^1 are the same or different and each represents a hydrogen or halogen atom or a straight- or

branched-chain alkyl or alkoxy group containing from 1 to 6 carbon atoms, p represents 0, 1 or 2, W represents a methylene group or an alkylene chain of 2 to 6 carbon atoms optionally substituted with one or more straight- or branched-chain alkyl groups of 1 to 4 carbon atoms, Y represents a 5- or 6-membered unsaturated ring containing 1, 2, 3 or 4 nitrogen atoms, optionally substituted by one or more substituents selected from straight- and branched-chain alkyl groups containing from 1 to 6 carbon atoms (which are each optionally substituted by a phenyl group), phenyl groups, amino groups and nitro groups, or a pharmaceutically acceptable acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/00023

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 403/12, 401/12, A 61 K 31/41, 31/415, 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	Patent Abstracts of Japan, Vol 12, No 40, C474, abstract of JP 62-187469, publ 1988-02-05 TAISHO PHARMACEUTICAL CO LTD --	1-2,5, 10-12, 14
X	Chemical Abstracts, vol. 111, no. 11, 11 September 1989, (Columbus, Ohio, US), M. Tsuji et al: "Preparation of (heterocyclyalkylthio- or -sulfinyl)diphenylimidazoles as antiulcer and anti-inflammatory agents", abstract 97243c & JP 01 40,467 (HISAMITSU PHARMACEUTICAL CO INC.) --	1-2,5, 10-12, 14
A	EP, A2, 0240015 (OTSUKA PHARMACEUTICAL CO., LTD.) 7 October 1987, see pages 1-4 and 62-68 --	1-4,11, 12,14

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
26th March 1991	18. 04. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	miss T. MORTENSEN

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	DE, A1, 3323870 (A. NATTERMANN & CIE GMBH) 3 January 1985, see pages 1-10	1-4,11, 12,14
	--	
A,P	EP, A1, 0359197 (E.I. DU PONT DE NEMOURS AND COMPANY) 21 March 1990, see pages 1-7 and 16-17	1-4,11, 12,14
	--	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 13 because ~~they~~ it relate to subject matter not required to be searched by this Authority, namely:

See PCT RUle 39.1(iv):
methods for treatment of the human or animal body by surgery or therapy,as well as diagnostic methods.

2. ☒ Claim numbers 1-7, 10-14 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

These claims are too broadly formulated to permit a meaningful search. The search has been limited to the compounds considered to be most relevant.

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/EP 91/00023

SA 43295

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 28/02/91
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0240015	07/10/87	JP-A-	1006271	10/01/89
		JP-A-	63045220	26/02/88
DE-A1- 3323870	03/01/85	DE-A-	3468021	21/01/83
		EP-A-B-	0130526	09/01/85
		JP-A-	60045563	12/03/85
		US-A-	4654358	31/03/87
EP-A1- 0359197	21/03/90	AU-D-	4136189	22/03/90
		JP-A-	2174762	06/07/90
		US-A-	4900744	13/02/90

For more details about this annex : see Official Journal of the European patent Office, No. 12/82

EPO FORM P0479